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*Biochemical Adaptations in Cardiac Muscle:
Effect of Exercise Training on Myosin ATPase Activity**

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Earlier reports from this laboratory have demonstrated that hearts of rats trained by prolonged swimming have improved mechanical performance under aerobic and hypoxic conditions. There was also discovered a direct relation between the total number of hours in the training program and cardiac actomyosin ATPase activity. The rate of superprecipitation of cardiac actomyosin was also significantly increased by training.

To investigate further the increased ATPase activity, myosin was purified from the hearts of rats made to swim 90 minutes and 2×75 minutes daily for 8 weeks. Ca^{++} ATPase activity was found to be increased in both the groups, the maximum increase being observed in the group made to swim 2×75 minutes daily. The Km for ATP, the Ca^{++} requirement, pH profile, and total sulfhydryl content all were similar in myosin from trained and control hearts. Myosin from each group had two light subunits with the same mobility on disc-gel electrophoresis. Myosin ATPase

from control but not from conditioned hearts was activated by increasing concentrations of KCl and ethylene glycol. Ten mM Iodoacetamide activated the ATPase from both the preparations, but the activation was greatest in the control myosin. There was a similar differential response to other sulfhydryl binding agents.

We next studied the fluorescence of heavy meromyosin (HMM), using 8-anilino naphthalene sulfonic acid (ANS) as a fluorescent probe. HMM from conditioned animals developed a 30% greater fluorescence with ANS as compared to HMM from control preparations. This difference was diminished when ATP was present (ATP binds to active site), and was abolished in the presence of ethylene glycol and urea (partial denaturation), or when EDTA was added (modifier of ATPase activity).

These studies support the assumption that physical training is associated with a conformational change at or near the active site of cardiac myosin. This change appears to involve the availability of sulfhydryl compounds. (*This work was supported by grants from the American Heart Association, New York, N.Y., and the National Heart and Lung Institute, Bethesda, Md.*)

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Mechanisms of Glucocorticoid Protection in Shock and Low-Flow States

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Various glucocorticoids, when administered in pharmacologic doses to animals and patients, are beneficial in the treatment of various experimental and clinical low-flow states. Several different mechanisms have been suggested to account for this protection in shock. However, at present, there is no agreement as to the precise mechanism(s) of such protection. The present study was undertaken to determine what role, if any, the microcirculation and vascular smooth muscle cells may play in such corticosteroid protection. Studies were designed to determine whether therapeutically effective (T.E.) doses of hydrocortisone sodium succinate (HC) and methylprednisolone sodium succinate (MP) alter precapillary arteriolar vessel diameters in the intact microcirculation and/or arteriolar reactivity to catecholamines (E, NE) and vasopressin (Vp) in the microcirculation. Both normal rat mesenteries as well as mesenteries of animals subjected to hemorrhagic and intestinal ischemia shock were examined *in vivo* with a high magnification (up to 4,000 \times) image-splitting TV-microscope recording system. (This system can resolve, accurately and rapidly, 0.02 of a micron change in microvessel lumen and/or wall size.) In addition, both HC and MP were examined *in vitro*

for their pharmacodynamic action on isolated rat aortic strips. The results indicate that although T.E. doses of HC (up to 300 mg./kg.) and MP (up to 60 mg./kg.) fail to alter microvascular lumen diameters of normal rat arterioles, both steroids effectively restore the severely constricted arterioles of shocked rats (>60% decrease in lumen) to 90%-95% of normal during as well as after steroid infusion. Both steroids were also found to dose-dependently inhibit E-, NE-, and VP-induced contractions as well as displace the log dose-response curves (DRC) to the right on *in vivo* arterioles as well as *in vitro* on arteries. In addition, both steroids reduce the magnitudes of calcium-induced contractions of depolarized rat aortic strips and cause a displacement of these DRC to the right. These data thus suggest that glucocorticoids may confer protection in shock and low-flow states by preventing the intense peripheral vasoconstrictor action of the many constrictor substances released in shock. This would result in: 1) an apparent but not real vasodilator action, and 2) a restoration of normal microcirculatory vasomotor hemodynamics. (Supported by N.I.H. Research Grants HL-12462 and HL-11391 and U.S.P.H.S. Career Development Award 5-K3-GM-38, 603 to B.M.A.).

A Model Program for the Control of Hypertension

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Hypertension affects 22 million Americans and contributes significantly to their mortality through cerebrovascular, cardiovascular, and renal complications. Effective means to lower blood pressure and prevent its lethal sequelae are available, but this therapy at present is not reaching 80% of hypertensive patients. This report describes a model applicable to community control of hypertension.

An experimental Hypertension Control Clinic has been established at the New York Hospital. There nurses guided by a specific protocol are primary providers of care. The experiment's goal is to determine the safety and efficacy of a simplified approach to the treatment of uncomplicated, asymptomatic hypertension.

Asymptomatic patients aged 25 to 55 are enrolled if they have not previously been treated and have blood pressures in excess of 160/95 recorded repeatedly. An initial physical examination is performed by a physician and nurse. All follow-up care is performed by the same nurse. Particular emphasis is placed on the education of

patients, streamlining the clinic visit, and frequent attendance early in treatment.

Experience with this hypertension control model, begun November 1, 1972, reveals that only 23 of the 37 patients referred had blood pressure levels meeting the acceptance criteria. Of 113 appointments scheduled, 101 were kept, 7 excused, and 5 were broken. One patient has left the program. To date, 70% of the patients have had a greater than 10% decline in systolic pressure and 25% have experienced a greater than 20% change. The diastolic pressure of one half the patients declined more than 10%. There have been no serious side effects of therapy.

This experimental treatment, measured by clinic attendance and blood pressure reduction, has proved satisfactory in 90% of the patients. To establish the full potential of this successful hospital-based pilot program, it must be evaluated in an outreach setting. (*This research project has been supported by a grant from the Esther and Joseph Klingenstein Fund, New York, N. Y.*)

Synthesis and Axonal Transport of Glycoproteins after Intracellular Injection of ^3H -L-Fucose Into an Identified Neuron in the Isolated Nervous System of Aplysia

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The marine mollusc *Aplysia californica* is a useful organism for studying basic molecular processes underlying neuronal function. The simple nervous system of *Aplysia* has several advantages over more complex ones; the neurons are large, they are reproducibly found from animal to animal, and single neurons can be studied by direct biochemical, morphological, and electrophysiological methods. We have used fucose to study the synthesis of membrane-associated glycoproteins and their subsequent transport along the axon of a single, identified neuron in the abdominal ganglion. When ^3H -L-fucose was injected by pressure directly into the cell body of the neuron, autoradiography revealed label only within the soma and processes of the cell. In contrast, when abdominal ganglia were incubated in ^3H -L-fucose, label appeared primarily over connective tissue and glia. At 4 and at 10 hours after injection, 64%

of the radioactivity in the cell body and 85% in the axon was macromolecular. Analysis of particulate glycoproteins by gel filtration followed by gel electrophoresis in SDS showed 6 major bands. Transported glycoproteins were similar to those remaining in the cell body, but one somatic protein did not seem to migrate. After 4 hours 22%, and after 10 hours 56% of the newly synthesized glycoproteins had moved into the major axon of the cell. Kinetics of transport were studied by cutting the axon into millimeter sections at various times after injection. Glycoproteins appeared to move, not as a single wave front, but rather as several distinct waves, the most rapid at a rate between 30 and 40 mm./day. This work is the basis for present and future studies on the formation of neuronal membranes and the axonal transport of membranous structures. (*Supported by the New York Heart Assoc., NIH, and NSF.*)

Analysis of the Inotropic Effect of Carbamylcholine in the Electrically Buffered Ventricle Strip in Frogs

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Contraction of frog ventricular muscle, like that of most atrial tissues, is profoundly depressed by cholinergic drugs. As in atrial tissue, this is associated with a marked shortening of the action-potential duration. To ascertain what mechanisms of electromechanical coupling might be involved, the time courses of transmembrane potential and of contractile force were recorded, by conventional means, from a frog-ventricle strip. To determine whether the negative inotropic effect is due entirely to the observed changes in transmembrane-voltage-time course or whether there exist additional components of the drug's effects which are not the result of these changes, an "electrically buffered" preparation was used. This was a thin (0.5 mm. diam. \times 4 mm. long) strip of frog ventricle, drawn through a hole in a rubber membrane. Less than 0.2 mm. of tissue extended forward from the membrane, and this was attached by a snare to a force transducer. The rubber membrane held the muscle securely, so that force was recorded only from the forward (short) segment. When carbamylcholine (CCh) was applied only to the for-

ward segment, the action-potential-time course was virtually unaltered, since the cable properties of cardiac muscle constrained the electrical behavior of the short segment to that of the more significant amount of tissue behind the rubber partition.

Application of 5×10^{-7} M CCh to both segments (i.e., to the entire muscle) reduced force of contraction, and its maximal rate of rise, by 40%. This was accompanied by a marked decrease in action-potential duration (750 to 300 msec.) with only minimal changes ($<3\%$) in the early time course of the plateau. Application of CCh to only the short segment reduced force of contraction by 10-20% and rate of rise of tension by 15-25%. Only minimal changes in action potential duration ($<6\%$) occurred.

Thus CCh appears to alter force of contraction by at least two mechanisms: one which is mediated through a reduction in the time-course of the action potential and, consequently, of time-to-peak tension; a second mechanism which is independent of membrane voltage but reduces rate of rise of tension. (*Supported by a Grant from the New York Heart Association.*)

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*Effects of Ouabain on the Pacemaker Current
in Cardiac Purkinje Fibers of Sheep*

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The therapeutic, positive inotropic effect of cardiac glycosides is complicated by their tendency to cause undesirable electrical activity. To study the mechanism whereby ouabain produces an increase in spontaneous electrical activity, we determined the effect of this glycoside on the magnitude and kinetic properties of the slow time-dependent outward current (I_{K_2}) considered to underlie spontaneous diastolic depolarization. A two-microelectrode, voltage-clamp technique was used.

Sheep Purkinje fibers were separated into short (1.6 mm.) segments by a method described elsewhere (*J. Appl. Physiol.* 34: 527-30, 1973). Preparations were superfused with oxygenated Tyrode solution ($[K]_o = 2.7$ mM.; $[Ca]_o = 2.7$ mM.) at 36° C. A. holding potential of -80 mv was imposed on the fiber. Hyperpolarizing voltage steps of 10 sec. duration were imposed on the membrane in 5 mV increments. The change in I_{K_2} corresponding to each voltage step was recorded under control conditions and after exposure to ouabain, 2×10^{-7} M.

After exposure to ouabain for less than 60 minutes the magnitude of I_{K_2} decreased at all potentials. This decrease was greater after exposure for more than 60 minutes. The time constants of deactivation of the residual I_{K_2} measured after 60 minutes tended to increase. The steady-state inward current increased after exposure for less than 60 minutes but decreased after more than 60 minutes. The voltage range in

which I_{K_2} is activated did not shift. The reversal potential tended to shift toward less negative values after 60 minutes. Partial reversal of these effects occurred within 60-90 minutes after removal of ouabain.

The decrease in magnitude of I_{K_2} in the presence of ouabain for less than 60 minutes resulted in an increase in inward current in the potential range in which spontaneous diastolic depolarization usually occurs and could account for the increased slope of spontaneous diastolic depolarization characteristic of the early stages of ouabain toxicity. The subsequent decrease in magnitude of inward current may be the result of accumulation of sodium in the fiber due to inhibition of the Na pump by ouabain. This could result in a decrease in the driving force acting on sodium at diastolic potentials. This effect could explain the loss of transmembrane resting potential characteristic of the latter stages of ouabain toxicity. An implication of these results is that some of the automatic rhythms seen in advanced stages of glycoside toxicity result from automatic foci located above the Purkinje system or that an ionic mechanism separate from that described for normal Purkinje fibers is able to cause spontaneous electrical activity in these fibers at depolarized levels of transmembrane potentials. (*Supported by NIH Grant HL-12738.*)

*Hypersensitivity Reactions of the Heart Induced by Penicillin
and Inhibition by Two Classes of Antihistamines*

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Clinical manifestations of acute hypersensitivity reactions include respiratory distress and cardiovascular collapse. Cardiovascular collapse need not be secondary to the asphyxiating effects of bronchospasm and laryngeal edema but might be directly related to primary cardiac events (e.g., ventricular arrhythmia or acute myocardial infarction). *In vitro* cardiac anaphylaxis supports this hypothesis (Feigen, G. A. and Prager, D. J.: *Amer. J. Cardiol.* 24:474, 1969; Levi, R.: *J. Pharmacol. Exp. Ther.* 182:227, 1972). Since penicillin is the most frequent cause of allergic reactions in man, we set up a model of cardiac anaphylaxis to penicillin. Guinea pigs were sensitized with benzylpenicilloyl-protein conjugates and their hearts were challenged *in vitro*. This resulted in an acute crisis of cardiac function which consisted of sinus tachycardia, atrioventricular conduction block, ventricular contractile failure, drop in coronary flow, and histamine release.

Since histamine is the major mediator of cardiac anaphylaxis, antihistamines were used specifically to antagonize this crisis. Both classes of antihistamines (anti-H₁ and

anti-H₂) were used, either alone or in combination. The release of histamine was not affected by either class of antihistamine. Chlorpheniramine (anti-H₁) at a concentration of 10⁻⁶M reduced the frequency and duration of conduction arrhythmias but not the sinus tachycardia; the coronary flow was improved. Burimamide (the newly developed anti-H₂) at a concentration of 2.7 × 10⁻⁴M antagonized the sinus tachycardia, but not the impairment of atrioventricular conduction or the decrease in coronary flow. Chlorpheniramine and burimamide in combination inhibited the sinus tachycardia, the impairment of atrioventricular conduction, and the decrease in coronary flow. These findings suggest that both classes of antihistamines (anti-H₁ and anti-H₂) are needed to antagonize the various effects of anaphylaxis of the heart.

This model should prove useful for the further testing of pharmacologic agents beneficial in hypersensitivity reactions to drugs. (*Supported by a grant-in-aid from the New York Heart Association and in part by NIGMS GM 00099.*)

Effects of Alpha-Adrenergic Blockade on Excretion of Sodium and Water in Normal and Caval Dogs

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It has been suggested that the sympathetic nervous system plays a role in the sodium retention of dogs with chronic thoracic inferior vena cava constriction and ascites (caval dogs). In the present experiments the alpha-adrenergic blocking agent phenoxybenzamine (PBA) was administered intravenously ($10 \mu\text{g./kg./min.}$) to 6 normal and 6 caval dogs during a steady-state water diuresis under anesthesia. In normal dogs a natriuresis was generally noted at 60 minutes after start of the PBA infusion and reached a peak plateau at 80 to 120 minutes. Sodium excretion ($U_{Na}V$) increased from 264.7 ± 56.0 (SEM) to $369.7 \pm 65.2 \mu\text{Eq./min.}$ ($p < 0.01$), and sodium clearance (C_{Na}) increased from 2.47 ± 0.22 to $3.58 \pm 0.47 \text{ ml./min./100 ml. GFR}$ ($p < 0.01$). In caval dogs sodium excretion did not change. $U_{Na}V$ was $33.5 \pm 8.3 \mu\text{Eq./min.}$ and C_{Na} was $0.44 \pm 0.11 \text{ ml./min.}$ in the control state (both values are significantly lower than in normal dogs, $p < 0.001$) and remained stable at $31.5 \pm 6.8 \mu\text{Eq./min.}$ and $0.41 \pm 0.01 \text{ ml./min.,}$

respectively, during the period corresponding to the peak natriuresis noted in normal dogs. In both groups urine volume, fractional free water clearance (CH_2O/GFR), and distal sodium load ($CH_2O + C_{Na}/\text{GFR}$) did not change significantly. However, in normal dogs distal tubular sodium reabsorption ($CH_2O/CH_2O + C_{Na} \times 100$) decreased from $73.3 \pm 2.8\%$ to $63.0 \pm 4.0\%$ ($p < 0.05$), with no change noted in caval dogs. In both groups blood pressure, GFR, effective renal plasma flow (C_{PAH}), and filtration fraction were essentially unchanged during PBA administration. These data demonstrate a natriuretic effect of alpha-adrenergic blockade in normal dogs with the major site of action in the ascending limb of Henle's loop. The absence of a natriuretic response to PBA in caval dogs suggests that increased alpha-adrenergic activity does not play a role in the sodium retention of these animals. (*This work was supported by N.I.H. grant HL-10914 and by a grant from the Kidney Foundation of New York and the Arnold Schwartz Fund for Education and Health Research, New York, N.Y.*)

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Evaluation of Peripheral Vascular Disease by Use of $^{133}\text{Xenon}$

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Peripheral vascular disease in 140 lower extremities using intramuscular and intracutaneous $^{133}\text{Xenon}$ with histamine augmentation was evaluated, measuring nutritive capillary blood flow and the time from release of arterial occlusion to maximum hyperemia ("T"), and correlating these with physical examination, angiography, and clinical course.

The following determinations were made:

1) The above described isotope washout method is clinically useful and reliable in measuring skin and muscle blood flow.

2) Muscle T and nutritive capillary flow correlated well with the extent of vascular disease.

3) Skin T also correlated well and, unlike that in normal individuals, increased distally in ischemic limbs.

4) Skin-blood flow at ankle and below knee levels correlated poorly with extent of disease, but flow at the dorsum of the foot correlated well.

5) Diabetics with tissue loss or claudication did not differ in flow or T patterns from their nondiabetic counterparts.

6) Relatively asymptomatic nondiabetic extremities were more severely affected

than were those of diabetics at all levels.

7) While the capillary flows and T values could not predict which diabetics with tissue loss would come to amputation in a given time interval, anterior tibial nutritive capillary flow may be a better prognosticator of healing after amputation than evaluation of arterial bleeding at surgery by an inexperienced operator.

8) Diabetics with neuropathies but neither claudication nor frank gangrene may suffer a "skin steal syndrome" which preferentially shunts blood to skin at the expense of muscle, possibly the result of an "autosympathectomy."

9) Normal-skin blood flow does not exclude the presence of chronic nonhealing ulcers unrelated to venous stasis disease in the lower extremities of diabetics.

10) Vasodilan appears to have no predictable effect on either skin or muscle blood flow as measured by this method.

11) In following individual difficult cases, the $^{133}\text{Xenon}$ washout method may be more reliable in obtaining reproducible information than other methods of clinical evaluation. (*This work was funded by the Kahn Research Funds, New York, N.Y.*)

*Glomerular Capillary Alterations in Streptozotocin Diabetes:
A Possible Animal Model for Diabetic Vasculitis*

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An adequate experimental animal model for human diabetes and its vascular complications is unavailable. In order to develop a laboratory model, Streptozotocin-induced diabetes was produced in Lewis rats by a single intravenous injection of 65 mk./kg. of Streptozotocin. This resulted in marked permanent hyperglycemia with fasting blood sugars ranging from 300-500 mg.%, glycosuria, polyuria, and weight loss.

Diabetic rats were sacrificed at monthly intervals. Heart, lungs, pancreas, kidneys, adrenals, small intestine, skin, urinary bladder, aorta, eyes, liver, and esophagus were examined by light microscopy. Animals diabetic for less than six months showed changes in the pancreatic islets and glycogen accumulation in the cells of the pars recta of the kidney. Animals diabetic for more than six months showed glomerular changes consisting of minimal focal segmental thickening of the glomerular basement membrane (GBM).

Ultrastructural studies performed on renal tissue of the animals diabetic for more than six months showed electron dense deposits in the GBM and in the mesangium. There was also focal extension of the mesangial matrix into the peripheral loops of the glomerular tuft. The focal thickening of the GBM was confirmed. Glomerular epithelial cells had prominent endoplasmic reticulum, cytoplasmic swelling, and focal fusion of the foot processes. Similar studies were performed on kidneys from age-matched nondiabetic controls. Only minimal abnormalities were observed in the control animals.

Streptozotocin diabetes of more than six months' duration in the Lewis rat may represent a useful model for studying the vascular complications of diabetes. Preliminary data suggests that ultrastructural analysis of renal tissue in these animals may reveal abnormalities which are specifically related to chronic diabetes. (*Supported by U.S.P.H.S. Grants 5 RO 1 HL 14799 and AM 12396 and NCI traineeship 5 TO 1-Ca05107-11 [CMF].*)

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Renal Hemodynamics During Cardiopulmonary Bypass

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The effects of cardiopulmonary bypass (CPB) on renal hemodynamics were studied in 8 dogs using $^{133}\text{Xenon}$ washout. A catheter was inserted into the right renal artery under fluoroscopic guidance via the left femoral artery and a bolus of 700-1000 μc of $^{133}\text{Xenon}$ injected. Washout curves were obtained with a collimator placed over the kidney before CPB, after 15 and 90 minutes of CPB, and after discontinuing CPB. Arterial blood pressure, urine output, and free water and sodium clearance were measured. Total CPB was undertaken at normothermia using venous gravity drainage, an arterial roller pump, a heat exchanger, and a Sci-Med Kolobow membrane oxygenator. The animals were sacrificed and the kidneys weighed.

Washout curves were analyzed by establishing regression lines and developing four components of renal blood flow (RBF) by subtraction: I cortex, II juxtamedulla, III inner medulla, and IV hilar fat. Percentage of total radioactivity and regional blood flow was derived for each component and total RBF calculated. No consistent changes in urine flow or osmolar or

sodium clearance occurred during CPB. However, significant alterations in both RBF and intrarenal-blood-flow distribution were observed.

RBF decreased progressively during CPB (338 control \rightarrow 321 after 15 min. CPB \rightarrow 236 ml./100 gm./min. after 90 min. CPB) and did not immediately increase after discontinuing CPB. After 15 min. of CPB, cortical flow (component I) was reduced from 774 to 676 ml./100 gm./min., a decrease in activity from 64 to 35% ($p < 0.02$). After 90 min. of CPB, cortical flow was less than 15% of total RBF. While juxtamedullary flow (component II) initially increased and then decreased during CPB, relative percentage activity increased from 28 to 47% after 15 min. of CPB ($p < 0.02$) and to 56% after 90 min. ($p < 0.02$). Inner medullary flow (component III) did not change during bypass. The decrease in total RBF with CPB was associated with an obvious shift from cortical to juxtamedullary regions. This alteration in flow is probably a factor in the pathogenesis of postoperative renal dysfunction. (*Supported by N.Y.U. Institutional Funds.*)

*Bedside Measurements of Extravascular Lung Water (ELW)
in Noncardiac Pulmonary Edema*

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Hemodynamic and ELW measurements were obtained on four patients admitted to the Intensive Care unit with grade IV acute pulmonary edema of noncardiac origin. Pulmonary artery (PA), pulmonary wedge (Pw), systemic pressure (Ao), cardiac index (CI), and pulmonary (PVR) and systemic resistance (SVR) were determined by means of Swan-Ganz and polyethylene catheters placed in the PA and aorta (AO) respectively. ELW was computed from indocyanine green and thermodilution curves obtained by injection of the indicators into the PA and sampling from the AO. Mean transit time was com-

puted by the gamma variable method (*Circ. Res.* 14:502, 1964). The validity of this nonisotope method was established in separate experiments in 9 dogs. ELW in these dogs by 1) thermodilution, 2) Cr⁵¹-labeled red cells and THO; and 3) dry-wet ratios, averaged 3.7, 3.5, and 4.1 ml./kg. respectively. For data on patients see table.

The data indicate a threefold increase in ELW, normal Pw and slightly elevated PA pressure, and CI in noncardiac pulmonary edema. The thermodilution method is of clinical value for the quantitative assessment of pulmonary edema.

	ELW	$\bar{P}A$	$\bar{P}w$	$\bar{A}o$	CI	PVR	SVR	PaO ₂
	ml./kg.	mm. Hg	mm. Hg	mm. Hg	l./m ²	d. sec.	cm. ⁻⁵	mm. Hg
	7	21	7	88	3.6	315	2,186	53
S.E. ±	2	3	2	13	1.0	92	667	4

*Changes in Coronary Sinus (cs) pO_2 and O_2 Saturation
Resulting from pCO_2 Changes*

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The constancy of cs O_2 during changes in myocardial O_2 consumption, heart rate, aortic pressure, cardiac output, and other physiologic alterations implies a primary role for O_2 in coronary-flow autoregulation. The stability of cs O_2 was stressed by varying pH and observing the effects on cs pO_2 , cs O_2 saturation, cs O_2 content, cs pCO_2 and myocardial O_2 extraction. In 15 dogs mechanical hyperventilation was performed for 15 minutes and simultaneous arterial and cs samples were taken during control, experimental, and recovery periods. In 5 dogs CO_2 in concentrations of 5 to 16% was added to inspired oxygen while similar blood samples were taken. CS pO_2 was not constant but varied from 8.2 to

96 mm. Hg while cs pCO_2 was changed from 15.6 to 96 mm. Hg, the best fit being a logarithmic one ($r = 0.87$). The cs pH varied from 6.97 to 7.71 units, and cs pO_2 displayed a logarithmic relation to cs pH. The cs O_2 saturation increased from 6.6% to 86% as cs pCO_2 rose, the relation also being a logarithmic one ($r = 0.75$). Myocardial O_2 extraction varied from 87% during hyperventilation to 12.8% with CO_2 breathing. This combination of high myocardial oxygen extraction, low cs pO_2 , and cs O_2 saturation during hypocapnia implies that O_2 delivery to the myocardial cell is compromised at this time. The data suggest that myocardial pCO_2 is a primary mediator of coronary autoregulation and an explanation for the occurrence of refractory ventricular arrhythmias in hypocapnic states.

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*Cryoproteins and Immune Complexes
in Acute Experimental Serum Sickness*

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Circulating immune complexes can deposit in host tissue, causing vascular injury including glomerulonephritis. We and others have reported serum cryoprecipitates in human immune complex nephritis. In rabbit-serum sickness, the classical model of immune complex disease, we have reported antigen along with specific antibody in serum cryoprecipitates, suggesting that cryoprecipitates contain immune complexes.

In this study we have examined this hypothesis by correlating cryoprecipitates with immune complexes in acute serum sickness produced in rabbits with I^{125} labeled bovine serum albumin (I*BSA). The amount of I*BSA in immune complexes was quantitated by the Farr technique.

Studies of the time course of I*BSA cryoprecipitation following a single intravenous injection of I*BSA were performed in 5 rabbits. I*BSA cryoprecipitation was not detected before immune complexes appeared in the circulation. It reached peak values while immune catabolism of I*BSA was occurring. The time course of serum cryoproteinemia paralleled I*BSA cryoprecipitation. Redissolved cryoprecipitates contained IgG, IgM, and BSA.

The quantity of I*BSA in immune complexes was measured in samples from 11 rabbits on days 9, 10, and 11. Determinations were made in triplicate before and after the serum was placed at 2° C. to allow cryoprecipitate to form. Seven animals showed significant I*BSA cryoprecipitation. In most

of these samples the quantity of complexed I*BSA was significantly decreased in the serum after cryoprecipitation. The decrease in complexed I*BSA correlated with the amount of I*BSA in the cryoprecipitate. As much as 50% of I*BSA in immune complexes could be removed from serum by cryoprecipitation.

Sucrose gradient ultracentrifugation studies showed that cryoprecipitates appear primarily when the fresh serum contains large molecular weight immune complexes.

Animals with marked cryoproteinemia had greater elevations in serum creatinine than animals with mild or absent cryoproteinemia. Redissolved cryoproteins were injected intravenously into untreated rabbits. IgG and BSA was localized in the glomeruli of these animals by immunofluorescence.

Ongoing studies of human renal disease corroborate our hypothesis that cryoprecipitates contain immune complexes which are of immunopathological significance. (*This study was supported by Grant AM 14928 from the National Institute of Arthritis and Metabolic Diseases, Training Grant HD 0051 [Dr. Griswold] and Grant HD 0093 from the National Institute of Child Health and Human Development, Bethesda, Md., and Grant in Aid from the New York Heart Association. The work was performed during a fellowship from the New York Heart Association [Dr. Koss] and during the tenure of an Established Investigatorship from the American Heart Association [Dr. McIntosh].*)

*The Effect of Unilateral Nephrectomy on the Renal Response
to Saline Loading in the Rabbit*

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Adaptive changes in renal sodium excretion serve to maintain sodium homeostasis in patients and experimental animals with significant reduction in nephron mass.

To examine the mechanism for this adaptation, and to determine whether the renal response to acute saline loading might be thereby altered, sodium handling was studied in New Zealand white rabbits before and 14 to 52 days after unilateral nephrectomy.

Fourteen male rabbits weighing 3 to 4 kg. were studied during the infusion of 0.9% saline at 0.075 ml./min., and following the infusion of 1.8% saline (0.75 ml./min.) for 1 hour. The urinary excretion rate of sodium (UNaV) and the excreted fraction of sodium (EFNa) during the final 30 minutes in the control period and the final 30 minutes of saline loading were compared.

The mean control UNaV pre-nephrectomy was 28.6 ± 11.7 μ Eq./min. The corresponding postnephrectomy value was 22.5 ± 18.4 μ Eq./min. ($P > 0.05$). The glomerular filtration rate (GFR) and the renal plasma flow (RPF) per kidney increased after nephrectomy from 7.1 ± 2.4 ml./min. and 23.6 ± 11.8 ml./min. to 12.0 ± 2.8 ml./min. and 41.7

± 13.5 ml./min. respectively ($P < .01$), while the EFNa (1.7 ± 1.0) did not differ statistically from that following nephrectomy (1.3 ± 0.9 , $P > 0.05$). Thus the adaptive change in basal sodium excretion was attributable to hemodynamic alterations, perhaps through hypertrophy, and not to changes in the tubular handling of sodium.

In response to acute saline loading, the UNaV increased to 79.5 ± 52.8 μ Eq./min. in pre-nephrectomy studies and to 82.4 ± 46.1 μ Eq./min. following functional adaptation ($P > 0.05$). In comparing individual animals postnephrectomy the extent of natriuresis did not correlate with the magnitude of the adaptive hemodynamic changes.

The results suggest that sodium balance following uninephrectomy in the rabbit is achieved largely by functional hypertrophy of the remaining nephrons, rather than a change in fractional sodium reabsorption. The renal response to acute saline loading does not appear to be altered by these adaptive changes. (*This study was supported by Research Grant HE 03272-15 from the National Heart and Lung Institute, Bethesda, Md., and Grant HL 15124-01 [CVB].*)

Blood Rheology in Acute Myocardial Infarction

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Serial blood rheologic measurements were made in 22 patients following acute myocardial infarction (AMI); measurements included hematocrit (HCT), plasma-protein concentration, and plasma and blood viscosity (η). Patients were divided into two groups on the basis of blood viscosity (shear rate = 0.5 sec.^{-1}) during the initial 24 hours; Group A (10 patients) had blood η above 50 cP, and Group B (12 patients), values below this level. Viscosity (η) was determined in a coaxial cylinder viscometer at shear rates of 0.01 to 400 sec.^{-1} . In Group A the initial blood η at all shear rates was about 50% higher than in Group B. Interestingly, the HCT range was 49 to 58% in Group A and 37 to 48%

in Group B. In Group A, blood η and HCT fell in the course of one week to levels not significantly different from Group B. In both groups, plasma η , fibrinogen, and α_2 -globulin were elevated in the first 24 hours, continued to rise during the first week, and decreased gradually thereafter. These changes were greater in Group A and contributed to the high blood η . Complications: e.g., shock, mental confusion, or thromboembolism developed during the first week in 6 of the 10 Group A (high η) patients and in none of the 12 Group B (low η) patients. This study suggests that elevation of blood η and even the simpler measurement, HCT, in the first 24 hours after AMI have prognostic value and therapeutic implications. (Supported by The New York Heart Association and the Scaife Family Charitable Trusts, Pittsburgh, Pa.).

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Intra-aortic Balloon Pumping in the Presence of Aortic Incompetence

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Intra-aortic balloon pumping (IABP) for the treatment of cardiogenic shock is commonly held to be contraindicated in the presence of an incompetent aortic valve. This study is designed to determine whether aortic regurgitation (AR) would indeed negate the effective mechanisms of IABP.

IABP was applied to three normotensive and two hypotensive, anesthetized, open-chest dogs, in which reversible and graded degrees of AR were created by a basket catheter in the aortic valve annulus. Measurements were made of: 1) aortic, left-common carotid, and left anterior descending (LAD) arterial phasic flows; 2) left-atrial, left-ventricular, and aortic pressures; and 3) ECG.

Twenty conditions of AR, before and after IABP, were analyzed. Regurgitant fractions were regulated between 17 and 69% (mean 40%). IABP increased both forward and regurgitant flow; however, the effective

stroke volume remained unchanged with moderate AR and increased 12% with severe AR. Despite the fact that IABP caused an increase in regurgitant flow, left-ventricular end diastolic pressures were unchanged. There was an average increase in aortic mean diastolic pressure of 23%. There were insignificant decreases in left ventricular mean systolic pressure and left ventricular peak systolic pressure.

In two dogs the LAD was ligated at its distal third, together with its accompanying branches, so as to create a relatively ischemic myocardium exhibiting minimal reactive hyperemia. IABP, in the presence of all degrees of AR, produced immediate and sustained increases in coronary flow. Carotid flow was insignificantly changed.

The improved effective stroke volume and large increase in coronary arterial flow thus demonstrate that IABP can be effective, even in the presence of aortic incompetence.

*Closed Chest Left Atrial-Femoral Bypass, A Superior Mode of Therapy
for Cardiogenic Shock: Experimental and Clinical Studies*

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Cannulation of the left atrium was performed, using a modification of Ross' trans-septal technique. An 85-cm., 28 French polyvinyl chloride catheter was inserted fluoroscopically retrograde through the femoral vein, across the atrial septum, and into the left atrium. Left atrial-femoral bypass was accomplished using a roller pump for suction drainage and various techniques of retrograde perfusion into the femoral artery.

Initial experiments in 10 normal dogs and 6 shock preparations employed nonpulsatile return flow into the femoral artery. Animals were maintained on bypass for periods of up to 8 hours. Long-term survival was accomplished in 4 normal dogs in whom complete closure of the artificially created atrial septal defect was demonstrated one month following catheterization. Using a nonpulsatile return pump, bypass flow rates of up to 95% of the cardiac output could be accomplished. Each of the shocked animals responded to bypass with hemodynamic stability, improved organ perfusion, and

cessation of arrhythmias. An additional 10 normal dogs were placed on left atrial-femoral bypass, using a Bentley pulsatile pump for arterial return. Synchronization of the pulsatile pump with the dogs' heart rate resulted in significant diastolic augmentation (12 to 15 mm. Hg).

Left atrial-femoral bypass with nonpulsatile flow was used for 8 to 24 hours in 3 moribund patients with cardiogenic shock. During perfusion, flow rates ranged from 3.5 to 5 l./min. and mean blood pressure could be maintained at 100 to 110 mm. of Hg without vasopressor support. Peripheral vasospasm subsided, and a copious diuresis occurred. No hematologic abnormalities developed and plasma hemoglobin ranged from 40 to 60 mg.%. All patients expired with profound shock after bypass was discontinued. This method seems aptly suited for patients in profound cardiovascular collapse following myocardial infarction. Further clinical application is planned. (*Supported by N.I.H., Rosenhirch Foundation, and S. J. Koff Foundation.*)

*The Hemodynamic and Metabolic Effects of Glucose Infusion
During Rapid Atrial Pacing*

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Rapid atrial pacing was performed prior to and following the infusion of glucose (G) in 15 patients with arteriographic evidence of ischemic heart disease and normal G tolerance. Anginal threshold (AT) was reduced, a mean of 7.6 ± 3.0 (SE) beats per minute ($p < 0.05$), following the administration of 30 gm. G in 30 minutes and double product at AT fell 18.5 ± 6.64 ($p < 0.05$). Lactate (L) production was present at AT prior to G: mean arterial-coronary sinus (A-CS) $L = -0.04$ mM/L ± 0.11 but was converted to extraction at AT following G: mean A-CS $L = 0.09$ mM/L ± 0.04 ($p < 0.01$). Arterial G and L rose 176

mg./100 ml. and 0.19 mM/L respectively ($p < 0.01$); A-CS G difference was 2.9 ± 8.5 mg/100 ml. at AT before G and rose to 9.6 ± 11.7 at AT after G ($p < 0.05$). Repeat studies were performed in 7 other patients with coronary disease using an equal volume of isotonic saline instead of G. AT, double product, A-CS G and L differences, and arterial G and L concentrations were not significantly different in the two pacing periods. The induction of hyperglycemia produces a decrease in the AT and double product at AT, accompanied by conversion of myocardial lactate production to extraction and increased G extraction.

Role of the Vagus Nerve in Transcapillary Pulmonary Fluid Exchange

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The effects of bilateral cervical vagotomy on extravascular lung water (ELW) were studied in 9 healthy mongrel dogs, anesthetized with sodium pentothal and breathing room air. ELW, arterial oxygen tension (PaO_2), pulmonary artery (PA), pulmonary artery wedge (P_w), and femoral artery (FA) pressures, cardiac output (CO), and pulmonary blood volume (PBV), were determined serially over a period of 90 min-

utes following vagotomy. ELW was computed from cardiogreen and thermodilution curves, using the gamma variable method of analysis. For results see table.

Systemic pressure remained unchanged throughout the study. Conclusion: the data indicates that the observed rise in ELW following vagotomy is mediated through altered capillary permeability.

	<i>ELW</i> <i>ml./kg.</i>	<i>p</i>	<i>PaO₂</i> <i>mm. Hg</i>	<i>PA</i> <i>mm. Hg</i>	<i>P_w</i> <i>mm. Hg</i>	<i>CO</i> <i>l./min.</i>	<i>PBV</i> <i>ml.</i>
Control	3.2		73	16/7	7	3.0	257
5'	4.4	<0.05	77	16/7	8	2.6	269
30'	3.9	<0.10	77	17/7	8	2.8	266
60'	4.5	<0.02	77	18/8	7	2.7	229
90'	5.6	<0.02	73	18/7	7	2.3	193

*Electrocardiographic and Serum Enzyme Changes
Following Coronary Artery Bypass Surgery*

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Serial pre- and postoperative ECGs were obtained on 50 patients undergoing coronary artery bypass surgery (CAB), 15 patients with aortic valve replacement (AVR), and 13 patients with mitral valve surgery (MVS). Postoperative infarction was defined as new Q waves on the postoperative ECGs. In the CAB group, infarction occurred in 5/50 patients (10%). Age, preoperative hypertension, or left-ventricular hypertrophy (LVH) on ECG did not correlate with infarction. Patients with infarction had more severe coronary disease than the noninfarct group (3.2 mean vessels with significant stenosis versus 2.4 in noninfarct group) and more extensive coronary bypass (3.0 versus 2.4). There was no difference in bypass time and 2/5 with infarction had aortic cross-clamping versus 24/45 without infarction. Postoperatively, 4/5 (80%) with infarction had an SGOT >200 and a CPK >2000, whereas 3/45 (7%) without infarction had this pattern.

Three of the fifteen patients (20%) undergoing AVR or double valve surgery had postoperative infarction. All had LVH on preoperative ECG versus 50% of those without infarction. Postoperative infarction did not correlate with total pump time or coronary ischemia time. One hundred per cent of those with infarction had an SGOT >200 and a CPK >2000, versus 2/12 (17%) without infarction. None of the 12 patients in the MVS group sustained postoperative infarction, and none had an SGOT >200 and a CPK >2000.

Infarction following CAB surgery is more likely with at least 3 vessel disease but appears to be unrelated to pump time or aortic crossclamping. Localized snaring or clamping of coronaries may be important. Postoperative SGOT and CPK correlate with ECG evidence of infarction. Infarction following AVR may be related to inadequate coronary perfusion in the face of LVH.

*Neonatal Blood Pressure and Flow Responses
to Interacting Peripheral Stimulations*

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Responses to the interaction between sciatic nerve stimulation (SNS) and changes in baroreceptor excitation were studied in 30 piglets (aged 1 to 26 days). The animals were anesthetized with halothane (0.25 to 0.5%) in a mixture of 50% N₂O-50% O₂, while being artificially ventilated. Blood gases and temperatures were monitored and controlled. Simultaneous recordings were made of arterial pressure (P), ECG, and carotid (CF), renal (RF), and femoral (FF) blood flows. Flows were registered by calibrated electromagnetic flow-probe meters. The sciatic nerve was dissected and cut distally before stimulation. Using a newly developed technique, a Swan-Ganz flow-directed catheter was inserted via the common carotid artery to the level of the carotid sinus for stimulation of the baroreceptor area (CSI). Bilateral common

carotid occlusion (BCCO) was used to inhibit input. Results showed an augmentation of high-frequency SNS pressor responses shortly before, simultaneously with, or directly after BCCO. However, low-frequency SNS depressor responses were variable, depending on the sequence of interaction. FF was decreased if BCCO was added to SNS, as compared to SNS alone. Patterns of flow in other beds were not as obvious. CSI caused a decrease in pressor SNS response when performed before, simultaneously with, or after electrical stimulation of the nerve. However, no significant augmentation was observed when CSI interacted with a depressor SNS. We conclude that the cardiovascular controlling system in the neonate is capable of occlusive or summated responses which are, however, not equal to adult pig responses.

Cholesterol Metabolism in Human Adipose Tissue

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Obesity is associated with increases of both body cholesterol and cholesterol synthesis. To examine cholesterol metabolism in adipose tissue, repeated subcutaneous adipose tissue needle aspirations were performed in hospitalized, lean hyperlipidemic and obese normolipidemic patients maintained in strict caloric balance. The cholesterol of isolated fat cells was determined by gas-liquid chromatography. In 124 adipose tissue samples (20 patients) the mean cholesterol was $12.8 \times 10^{-4} \mu\text{g}/\text{cell} \pm \text{S.D. } 2.9$ and correlated well with cell size ($r = 0.86$) but not with age, sex, plasma cholesterol, or type of hyperlipidemia. The cholesterol was 92 to 95% unesterified and more than 75% of cholesterol was recovered in the intracellular oil droplet. In 3/6 nonobese patients, adipocyte cholesterol rose slightly but significantly when dietary carbohydrate was isocalorically substituted for polyunsaturated fat.

Serial adipose tissue sampling after a single intravenous ^{14}C -cholesterol dose in 9 nonobese patients consistently showed adipose tissue-cholesterol specific activity

crossing plasma specific activity at adipose tissue's highest point (4 to 6 weeks) but then decreasing at a much slower rate than plasma for up to 20 weeks.

Adipocytes from 5 obese patients were incubated with ^{14}C -glucose or ^3H -acetate. *In vitro* cholesterol synthesis rates were equivalent to 1 to 2 mg. cholesterol/kg. fat/day as compared to the 20 mg. cholesterol/kg. excess weight/day found previously *in vivo*.

Conclusions: 1) Adipocyte cholesterol is primarily determined by amount of triglyceride per cell but may fluctuate within narrow limits according to dietary composition. 2) Adipocyte cholesterol turnover is much slower than plasma cholesterol turnover. 3) Adipocyte cholesterol synthesis *in vitro* cannot explain the increased body cholesterol synthesis seen in obesity.

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Cholesterol Metabolism During Neomycin Therapy

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It has been known for many years that oral neomycin is a hypocholesterolemic agent. The present study was undertaken to assess further its mode of action.

The effect of 2 gm./day of oral neomycin on cholesterol (Ch) metabolism was studied in 4 patients by sterol balance and isotope kinetic techniques. Ch absorption was measured by 2 methods before and during neomycin therapy.

The drug caused a significant fall in plasma Ch (mean 25%, range 18 to 31%), while plasma triglycerides decreased in 1 patient only. During neomycin therapy there was a marked decrease in Ch absorption in all patients (by Method I, mean 22%, range 14 to 32%; by Method IV, mean 32%, range 22 to 46%). Fecal neutral steroid (FNS) excretion during the steady state increased significantly (mean 347 mg./day, range 323-353 mg./day) whereas bile acid excretion remained unchanged in 3 of the 4 patients. None developed steator-

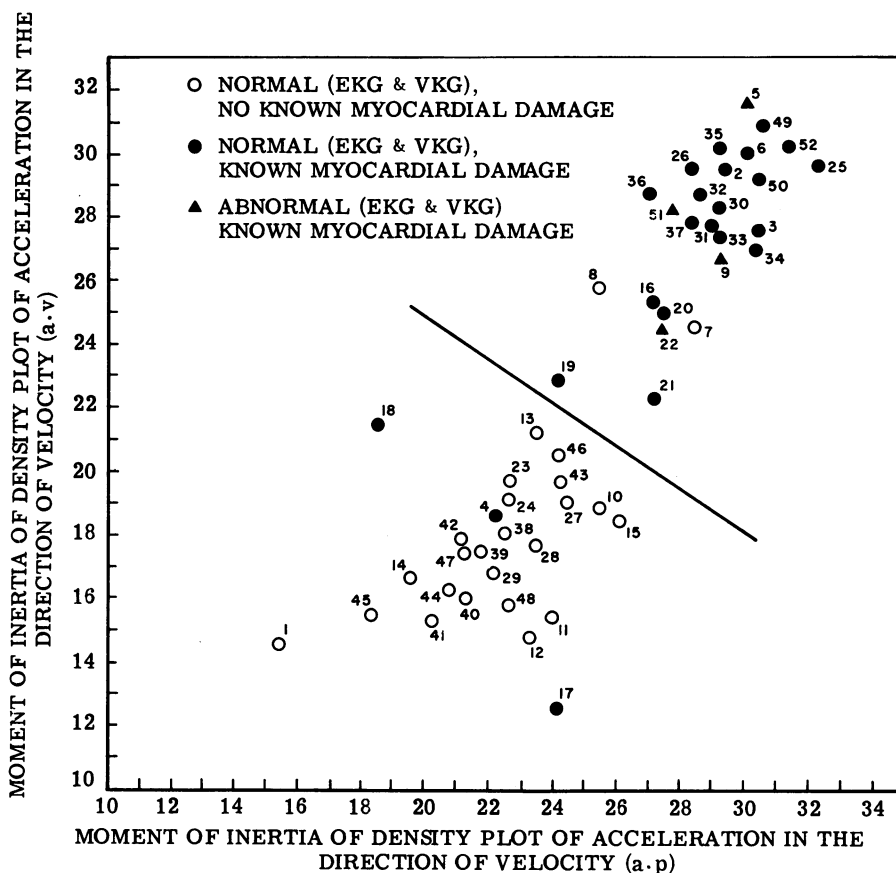
rhoea. Slopes of the plasma Ch specific activity decay curves were unchanged when neomycin was started in the 3 patients labeled with ^3H Ch intravenously. Toxic manifestations of neomycin were not observed (normal audiograms, urinalyses, and tests of renal and hepatic function).

It is concluded that oral neomycin in small doses increases FNS excretion and lowers plasma Ch concentrations with little effect on fecal bile-acid excretion or the plasma triglycerides. The increase in FNS excretion is due to Ch malabsorption. The absence of steatorrhoea indicates that malabsorption is not generalized. All patients were considered to have increased Ch synthesis or tissue efflux of cholesterol while on neomycin. (*This study was supported by Grant HL 0622 from the National Heart and Lung Institute and Grant FR00102 from the General Clinical Research Centers Branch, Div. of Research and Resources, Bethesda, Md.*)

Tangential Acceleration from QRS Vector Loop

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It is well known that myocardial damage may exist in the presence of a normally appearing electrocardiogram and vectorcardiogram. We are presenting a new method for diagnosing heart damage when the electrocardiogram and vectorcardiogram are normal. The new method depends on the computer rendition of acceleration from the ARS vector loop in the direction of its velocity and/or position vector. This

is termed tangential acceleration. When tangential acceleration is plotted against peripheral distance along the vector loop higher order acceleration components are demonstrated than when similar plots are made from QRS loops of normal individuals.

For this purpose the Orthogonal Frank lead system was employed. The QRS complex was recorded on analogue tape and

then digitized at a rate of 25 khz. The digitized data were then smoothed by a 6-pole Butterworth filter with a cutoff at approximately 1.5 khz. First and second time derivatives were then computed for the x, y, and z components of the BKG vector.

An initial examination of the acceleration vector presented visually in a number of different forms for a number of cases suggested that its spread about mean value was greater in the diseased than in the normal patient. Analysis of data for our first 77 records—40 diseased, 37 normal patients—shows that parameters measuring this spread are very promising for detecting cardiac pathology.

It has been shown that wide band record-

ings of the electrocardiogram produce similar results to computer methods of measuring tangential acceleration from the QRS loop in the direction of the velocity vector. (Langner, P. H., Jr., Glazelowitz, D. B., and Briller, S. A.: Wide band recording of the electrocardiogram and coronary heart disease. *Amer. Heart J.* 86:302-17, 1973.) However, although computer methods are more expensive, they appear to be more accurate than wide band recordings.

The figure is reproduced by permission from Seiden, E.G. and Stahl, C.: A new method for diagnosing myocardial damage in patients with normal electrocardiograms and vectorcardiograms. *Trans. N.Y. Acad. Sci.* 35: 283-303, 1973. (*This work was supported by U.S.P.H.S. Grant CD-00302*).

*The Contribution of Cerebral Hemorrhage to Mortality from Stroke
in New York City Blacks*

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Of 527 unselected black stroke patients in an inner-city hospital, 18% had non-aneurysmal intracranial hemorrhages, with a case-fatality rate of 75%. In the whole series there were 216 in-hospital deaths, of which 35% were due to hemorrhage. In patients aged 65 or less, fully 53% of 90 fatal cases were hemorrhagic, but only in patients below 46 years of age did hemorrhage account for more deaths than infarction. The mean age of patients with fatal hemorrhage was 61.5 years. The incidence of nonaneurysmal intracranial hemorrhages was higher than that in three white American and one black African series, and lower than that in one black African series. The same relation was true of the proportion of in-hospital fatalities due to nonaneurys-

mal hemorrhage. The differences, however, were not dramatic, and could be explained by varying definitions and hospitalization patterns. When the in-hospital mortality pattern is hypothetically extrapolated into annual mortality estimates, it appears that in New York City blacks spontaneous non-aneurysmal intracranial hemorrhage: 1) does not account for many more deaths than infarction; 2) is not much, if at all, more common or more lethal than in whites; and 3) does not occur predominantly at earlier ages than in whites. (*This study was supported by Health Services and Mental Health Administration Grant RM-0058 via the New York Metropolitan Regional Medical Program Grant 68-70.*)

Cardiovascular Effects of Propranolol and Practolol in Puppies

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Previous studies of the beta blocking agents, propranolol (PROP) and practolol (PRAC), in adult subjects suggest that PRAC does not have the marked negative inotropic effect of PROP at higher dosage. The immature circulation has recently been shown to display even greater sensitivity to PROP, whereas the effects of PRAC are unknown. In order to investigate the effect of PROP and PRAC in immature subjects, dose-response curves were studied in 11 (PROP) and 10 (PRAC) intact puppies (1.4 to 1.8 kg.), anesthetized with chloralose and morphine and maintained on a volume respirator. Beyond beta blocking levels (0.3 mg./kg.), defined by the absence of response to isoproterenol, PROP continued to depress heart rate (H.R.), cardiac index (C.I.), LV dp/dt and dp/dt/p. At 2.1 mg./kg., C.I. averaged 66% of C.I. at blocking levels (90 ml./kg./min. vs. 135 ml./kg./cm.) and LVEDP increased, in-

dicating a profound negative chronotropic and inotropic effect of PROP in large doses. Beta blockade with PRAC was achieved at a dose level of 1.2 mg./kg. In contrast to PROP, larger doses of PRAC (to 8.4 mg./kg.) did not cause further depression of LV function. Starling ventricular function curves, (4 PRAC, 4 PROP), with H.R. paced at 180/min., confirmed the above observation. After 2.1 mg./kg. of PROP (7× blocking dose), C.I. averaged 53 ± 13.0 cc./kg./min. at an EDP of 14.5 mm. Hg, while after 8.4 mg./kg. of PRAC (7× blocking dose), C.I. averaged 238 ± 31.3 cc./kg./min. at an EDP of 14.0 mm. Hg ($P < 0.01$). These results suggest that PRAC is a safer agent for induction of beta blockade in infants and children. (*This work was supported by Grant 5T01-HE05389-13 from the National Heart and Lung Institute, Bethesda, Md.*)

Mixed Lymphocyte Cultures in Rheumatic Fever Patients

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The major histocompatibility loci (HL-A loci and, in experimental animals, the mixed lymphocyte reaction locus) have been shown to be related to immune responsiveness and the tendency to develop certain diseases. While it appears 1) that rheumatic fever is a disease of abnormal immune responsiveness to the streptococcus, and 2) that rheumatic individuals may have a genetic predisposition to the disease, the nature of the process and the exact genetic factors involved have not as yet been demonstrated. In an effort to further delineate the possible relation between histocompatibility antigens and rheumatic fever, mixed lymphocyte cultures were undertaken between unrelated normals and pairs of unrelated patients with a well-documented past history of rheumatic fever. One million responder cells

were cultured in the presence of 1 million stimulator cells treated by mitomycin-C to prevent DNA synthesis. The amount of blastogenesis induced in the responder cells was gauged at the end of one week's culture by the amount of incorporation of ^{14}C -labeled thymidine.

It was found that while rheumatics respond well to normals, they are poor stimulators for both normals and unrelated rheumatics, irrespective of age, sex, ethnic group, HL-A type, and date of last attack of rheumatic fever. Whether this represents a lack of antigens on the surface of the rheumatic patient's lymphocytes or whether it represents a blocking of such surface antigens is as yet unclear, but preliminary data suggesting that a blocking phenomenon is at work will be presented. (*This research has been supported by Grant HL-03919 of the National Institutes of Health and a grant from the New York Heart Association.*)

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*Intrinsic Differences in Lipid Transport Rates
Through Proximal and Distal Small Intestinal Wall in the Rat*

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Restrained, unanesthetized rats absorb triglycerides at steady rates when the emulsified lipids are continuously infused intraduodenally. The lipid content of the intestinal wall during maximal steady state absorption is related to the transmucosal lipid transport rate.

Control animals showed regional differences in lipid- ^{14}C accumulation in small intestinal tissue after 3 hours of maximal triolein- ^{14}C absorption. When the washed small intestine was divided into 10 segments (duodenum = segment 1), segment 7 contained the most lipid- ^{14}C , of which >90% was triglyceride, and large lipid droplets were visible histologically inside the mucosal cells. This suggested that distal intestine was relatively less able than proximal intestine to release chylomicrons. The lipid-accumulation pattern (low proximally and high distally) was resistant to alteration by dietary or surgical manipulation. Direct infusion of fatty acid and monoglyceride for 7 days into segment 7 (substrate induction) failed to reduce the lipid- ^{14}C accumulation in this region after subsequent triolein- ^{14}C infusion. Con-

versely, after total starvation for 3 days there was no increased accumulation in proximal segments during maximal rate absorption. Surgical removal of segments 2, 3, 4, and 5 to expose distal intestine to upper intestinal luminal chyme did not increase the transmucosal transport rate; when triolein- ^{14}C was infused at least one month after proximal resection, the lipid- ^{14}C content of the original segment 7 remained high. Further, when proximal and distal luminal environments were exchanged, without reduction in intestinal length, by transposing segments 2 through 5 with segments 6 through 9, major lipid- ^{14}C accumulation still occurred in the original segment 7 during triolein- ^{14}C infusion one month later.

Since most properties of distal intestine known to show adaptive change are maximally adapted one month after operation, the results suggest that mechanisms controlling chylomicron release to intestinal lymphatics may be intrinsically different in proximal and distal small intestine. (*This study was supported in part by the New York Heart Association and Grants AM 05499 and AM 13436 from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.*)

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